genicity data to extrapolate to man. The net result of all of these differences suggests to me at least that the laboratory animal is not a sensitive indicator of carcinogenicity in tests with environmental chemicals. If results from laboratory animal tests are to be used to set up guidelines to protect very large human populations it is prudent to be extremely conservative in trying to apply this extrapolation.

Another way of looking at this is shown in Fig. 7. Some of you may have read an article in *Science* about seven years ago about some behavioral scientists who had been studying LSD in the cat and wished to see what happened in the elephant. They gave the mg/k dose of LSD which provided whatever behavioral response they wanted in the cat to an elephant borrowed from one of the local zoos. The result in a relatively few minutes was a very, very large elephant convulsing, defecating, and finally dying. What I would like to suggest is that we must not forget this principle of comparative pharmacology and toxicology as we try to extrapolate data from laboratory animals to man, or we may be associated with a very large convulsing and defecating elephant.

Fig. 7. "I just got tired of rats and mice, rats and mice."

Safe Dose? Problem of the Statistician in the World of Trans-Science

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When the statistician works on an issue in the public arena he often finds that the data he collects, and the manner in which he analyzes the data are conditioned by things outside his own professional competence. This paper gives some examples that attempt to discuss what the statistician might do that despite these pressures he might provide, if not an unbiassed picture, at least a fuller picture. Because I am from the National Cancer Institute, I am mainly concerned with the problems of what causes cancer, how we determine that a material is a carcinogen, and the statistician's role in establishing "safe" doses, if there are such things.

The statistician is constrained by the biological models of his laboratory colleagues. If the research worker with whom you are working is of the opinion that there is threshold in carcinogenesis, i.e. there are some doses that are sufficiently low so that they will not produce any cancer whatever, then it is extremely likely that he will design experiments

(consciously or unconsciously) that will yield data that point to the existence of a threshold. If on the other hand, if the biologist with whom you are working is a man who questions the threshold concept, his data likely will be developed in such a way as to demonstrate that the probability of a threshold is either extremely unlikely or data are of such a nature that you can't demonstrate whether a threshold exists or not.

If there are difficulties in unravelling threshold in the laboratory, the difficulties are multiplied many fold when we try to interpret the results of exposures of humans to potentially harmful materials. I will give an example from asbestos exposure. Asbestos hazards have been in the headlines recently and much work, some of it of very high quality, has been done. In reviewing the published papers in the relation between human asbestos exposure and the possible development of cancer, I found that two authors, McDonald (1972) and McDonald *et al.*, (1971) of McGill University in Canada and Enterline *et al.* (1972, 1973) of the University of Pittsburgh in the U. S., have attempted to develop a quantitative dose response relationship. McDonald and Enterline have used the same measure of exposure, millions of particles per cubic foot years (MPPCF years). A physical measure was taken of the number of particles present in a sample of air in the vicinity of the worker and then this multiplied up by the number of years that the worker was exposed at those levels. There are difficulties in such a dose measure. Workers are not at the same job all of the time, the levels of exposure are not the same all the time, and, thus, the dose for any specific worker is only an approximation. Further, there is always the problem that not all the particles measured in their millions of particles per cubic foot years are asbestos particles. Asbestos is a very difficult material to identify and measure in its submicroscopic state. Of all the papers I have read these two authors are the only ones who have attempted to quantify dose to give a dose response relationship.

There are some differences between McDonald's and Enterline's studies. McDonald's population is a population of working asbestos miners in Canada. Enterline's population is a population of retired industrial asbestos workers in the United States. McDonald measures his response in terms of equivalent average death rate. Enterline measures his response in terms of standard mortality ratio. I don't know how to equate these two. In the figures here, I attempted to put them on the same scale. Fig. 1 gives the mortality rates for cancer of the bronchus and lung for McDonald's measure of equivalent average death rate and for Enterline's measure standard mortality ratio. I have equated equivalent average death rate of 10 with a standard mortality ratio of 100. This is very likely to be wrong. I don't know what to equate in the equivalent average death rate to standard mortality ratio. In Fig. 1 the standard mortality ratio is 10 times the equivalent average death rate.

Fig. 1 shows two dose response curves of roughly the same shape. The solid line is fitted to the solid dots; those are the McDonald data. The dashed line is fitted to the x's, the Enterline data. In one paper, Enterline combined the three doses under 125 mppcf years, into one single dose group and that is shown on the figure by an x in a circle.

Because of the problem of equating equivalent average death rate to standard

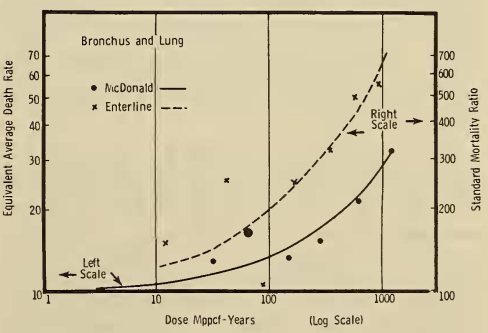

Fig. 1.—Mortality rates for cancer of bronchus and lung.

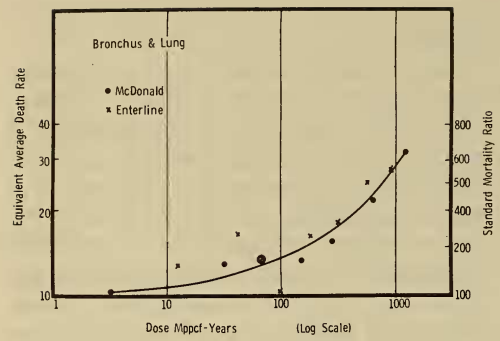

Fig. 1A.—Mortality rates for cancer of bronchus and lung, with scale changes (see text for details).

mortality ratio and because these two dose response lines don't seem to lie together, I have modified Fig. 1 into Fig. 1A. Here I have squeezed the standard mortality ratio scale down by a factor of two. I have taken the equivalent average death rate of 20 to equal a standard mortality ratio of 400, equivalent average death rate of 40 to equal a standard mortality ratio of 800 and so on. With this scale change on Fig. 1A, it looks as if a single response curve might be fitted to all the data. The McDonald and the Enterline data now don't seem far apart. As I have drawn this figure it looks as if there could possibly be a threshold in the vicinity of dose of under 10 mppcf years, although this is really quite uncertain. Concerning the possibility of threshold, McDonald says "The excess was virtually confined to persons with a dust index of over 200 mppcf years." Enterline says "There appears to be no direct relation between dust exposure and respiratory cancer below 125 mppcf years. Important increments in respiratory cancer mortality apparently occurred somewhere between 100 and 200 mppcf years."

It is difficult for me to talk about excess with respect to McDonald's data because his measure of the equivalent average death rate essentially has no "normal" against which to measure excess. Enterline's standard mortality ratio measure does give an opportunity to measure excess and I find it interesting that all his points below a dose of 100 lie above the standard mortality ratio of 100. These all indicate an excess mortality. There is no question that Enterline's statement that there is no direct relationship between exposure and respiratory cancer below 125 mppcf years is correct. Should the data above 125 mppcf have any effect on what one says about what happens below 125 mppcf? At least two interpretations are possible of these sets of data. One: there is a threshold (although it is chancy). Two: there is no threshold shown.

To examine the threshold concept a little further, I have reproduced Enterline's data in a table. Table 1 shows the dose, the standard mortality ratio at this dose and the 95% confidence limits on the standard mortality ratio. I have both combined the three lowest doses as Enterline has done and also presented the 3 lowest doses separately. We have equivocal results. With the 3 lowest doses combined there is a standard mortality ratio of 166.7; the confidence limits on this standard mortality ratio range from 93 to 275. Since 93 to 275 includes 100, one can say that these lowest doses are *not* different from 100. On the other hand, with an upper confidence as high as 275, the data are consistent with a substantial effect.

Have we demonstrated no excess for these three lower doses or have we only shown problems concerning the small number of persons exposed at the three lower doses? Was follow-up as good for the short-term workers (who then got low

TABLE I

Dose MPPCF Years	Standard Mortality Ratio	95% Confidence Limits on SMR (Haensel, 1962)
<25	153.8	18–555
25– 62.4	166.7 { 258.1	93–275 { 112–509
62.5–124.9	108.7	35–253
125–249.9	250.0	129–437
250–499.9[a]	326.9	lower limit
500–749.9	500.0	well over
>750	555.6	100

[a] This is given as 400 by Enterline, but that appears to be a misprint.

doses) as for the longer term workers who got the higher doses? Should the people in the regulatory agencies be suspicious of a result that has such a high upper confidence limit or should they say that since no significant excess has been demonstrated, that a safe level has been demonstrated?

The data given so far are concerned with problems of the inhalation of asbestos. There is more current concern over ingestion from water, or food. We would like to find out what happens when asbestos gets into the digestive system. On Fig. 2 are the data from McDonald

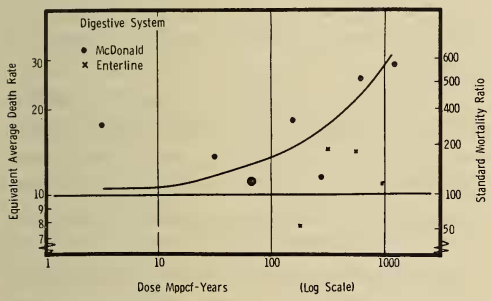

Fig. 2.—Digestive system cancers vs. exposure.

and Enterline showing the digestive system cancers vs. exposure. There were far fewer digestive system cancers reported then bronchus and lung cancers in this group of workers. The data show a wider range of fluctuation. In the McDonald data there are at least 2 inversions. Yet at his lowest dose level, somewhere between 1 and 10 mppcf years, he has an equivalent average death rate well above 10. The Enterline data also show some inversion. I plotted Enterline's 3 lowest points as he has done into a single point, an x with a circle around it. The next highest dose shows a standard mortality ratio of under 100. If there were a threshold fluctuation in sampling would give some rates below 100. The next two doses show SMR's over 100, and the next dose shows a lower standard mortality ratio, an inversion.

What could one say from these data? The McDonald data seem to say that inhaled asbestos, which then gets into the digestive system, is quite likely a digestive system carcinogen. The Enterline data lead to no such clean conclusion. To try to make more sense of these data I have combined some of the dose groups within each set. It seems to me that there is nothing sacrosanct about one particular dose range as compared to another, hence my dose groups are as "valid" as any.[1] The effect of combining various dose groups is shown on Figure 2A. The

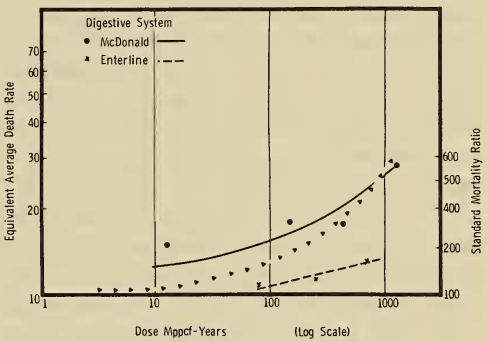

Fig. 2A.—Digestive system cancers vs. exposure, showing effect of combining various dose groups (see text for details).

dose response curve that was on Figure 2 is now shown on Figure 2A as the line made up of small triangles. The McDonald points, which in Figure 2 comprised six dose groups, have been collapsed into four. Enterline's data which comprised five dose groups have now been collapsed into three. The McDonald data now show a distinct dose response relationship lying well above the equivalent average death rate of 10 which I have previously suggested was "normal." The Enterline data show a dose response curve below, but perhaps paral-

[1] This is not strictly true. William Cochran (1968) discussed this problem in a Rietz Lecture published in 1968 in *BIOMETRICS*. My colleague, John Gart, has given me some references (Connor, 1972; Gart, 1971; Hamilton, 1974) showing how to compute a dose-response relationship for data like these without combining data into groups. One needs to have the individual data, of course. I will suggest Gart's approach to both McDonald and Enterline.

lel to the McDonald's, but still lying above the standard mortality ratio of 100. Are these data consistent with a threshold? McDonald's data are not consistent with a threshold. The Enterline data could be. If one continues the straight line that I have drawn for the Enterline data, it would come down to or cross the standard mortality ratio of 100 line somewhere between 10 and 100 mppcf years.

What have I shown here? Even a set of rather well collected data can be looked at in several different ways. The different ways might lead one to exactly opposite conclusions with respect to the important question of whether some human data have or have not demonstrated the existence of a threshold. Since when one is concerned with establishing the existence of the "safe" dose, one must be able to establish the existence of a threshold, it then seems to me that the statistical problem of establishing a "safe" dose becomes effectively an unsolvable problem. This puts us into the field of trans-science in the Alvin Weinberg sense (Weinberg, 1972). There is not much that we can do within science to answer that particular question. We must go on and look at some other ways to handle and solve this issue of so-called "safe" doses.

As statisticians we try to "model" the real world. The statistician in looking at a dose response relationship often finds that he is working with one of several mathematical models—in biology, usually one of three models. The probit model makes the assumption that the response is linear (as the integrated normal curve) against the logarithm of the dose. The second model is generally the logit model and it derives in part from certain kinetic considerations. The third model is the so-called "one-hit" model. This model postulates that one event is all that is necessary to create an activity and that this activity leads to an observable response. In the most extensive studies of radiation as a carcinogenic process, research workers and the technical reviewers seem to have come to an uneasy agreement that the one-hit model represents what is going on there. The appropriateness of the model becomes an issue that is not solvable by the statistician alone. Whatever model the statistician uses for his dose response model must have reality in the biology. And the statistician is not the judge of what is the reality in the biology, though his opinions are valid. He has to pay attention to those people who say that it takes some minimum number of molecules, not a single molecule to produce an effect. He has to pay attention to those theorists who would define cancer as a irreversible, self-replicating change. That is, once an event occurs it causes a change, perhaps a change in the genetic material of the cell, and this is self-perpetuating. That's very close to a one-hit concept.

However, no matter what the reality of the biology, these three major mathematical models of the biological dose response give, in the real experimental world nearly identical results for most of the dose range. In the range in which most work is done and given the size of most experiments, these models are indistinguishable. In a paper by an advisory committee of the Food and Drug Administration (FDA, 1971), the three models were compared over a 256-fold dose range over which they were nearly identical. Differences occur when one tries to extrapolate to the very low doses. In general the probit model has the highest order of contact; the one-hit model the lowest order of contact. The probit model having the highest order of contact, it says that the dose that it takes to produce a 1 in 1 million effect is higher than the dose that the logit or one-hit model would call for. Therefore, the model that one chooses is of considerable consequence when one wants to talk about responses at very low doses. And, of course, in the environment to which we are exposed, for most people we are concerned about very low doses. It does not seem to me at this time that it is possible for us to choose among these three models down at the very low doses. In fact, as a statistician wandering in biology, I am convinced that none of these models is ap-

propriate at very low doses. Certainly not for the heterogenous human population.

Whichever of these models one chooses, one is usually working in a yes-no situation. The statistician analyzes data after someone else has decided that there is a tumor or there is not a tumor. The pathologist says an animal has a tumor or the animal does not have a tumor. It is to this kind of situation that these three common mathematical models pertain. Usually there is more information in an experiment, i.e., the time-to-appearance of the tumors. Early work by Druckrey (1967) of Germany related the time-to-appearance of tumors to the dose of the carcinogen. The larger the dose the earlier the tumor and the shorter the so-called "latent" period. If we could take advantage of this kind of information, perhaps we could demonstrate that with very low doses the tumors might be expected to appear so very late in a lifetime as to be of no consequence. Albert and Altschuler (1973), starting with the Druckrey concept have attempted to produce a time-to-appearance model carcinogenesis. Their work was published in the Proceedings of a Hanford Symposium and generally is not easily available. This is unfortunate because more people should exploit this model to see what it implies. In its present stage of development the model has some flaws. Their time distribution for the appearance of tumors has been questioned. They use the lognormal distribution and several people (Pike, 1966; Peto *et al.*, 1972) disagree that this is the appropriate distribution. Gehan showed that it has a peculiar hazard function (Gehan, 1969). Albert and Altschuler considered the problem of the median time-to-appearance of tumors. This is inappropriate if we want to extrapolate to man. What we want to know is the time-to-appearance of the tumors in some very small per cent of the population, i.e. 1/10% or 1/1000%, etc. Finally, theirs is an estimating, or extrapolation model, and we need a way to put in a "guarantee" that the risk shall not exceed a certain amount. Mitchell Gail (1974) of the National Cancer Institute looking at the data on the study of the United States veterans with respect to lung cancer and smoking found lung cancer, if it were the only cause of death (as in an Albert/Altschuler computation) would have a mean time of appearance of about 320 years. But lung cancer is a serious problem because a good deal of lung cancer appears long before the age of 320.

The Albert/Altschuler work considers the life shortening effect of cancer not just the appearance or non-appearance of cancer. Since everyone must die at some time, the fact that a dose of a material produces a given number of additional cancers is not of as much consequence as if it produced that many cancers (or even fewer) at young ages. David Hoel and colleageues (1972) have done some work on this problem. Mitchell Gail attempts to estimate what he calls "three measures of merit." His first measure of merit is the actual life shortening that would occur in the whole population—given a new form of cancer or given that cancers appeared at some given age in the population and in some proportion of the population. Dublin and Lotka many years ago showed that all of the cancers in the population in the United States would reduce average life span somewhat of the order of less than 2 years. The second measure of merit is the life shortening for those people who develop cancer. For these people the shortening is a good deal greater. It ranges from 12 to 15 years more or less depending on the nature of the cancer. Finally, Gail (1974) adds another measure of merit. This measure of merit is the one of directly asking what does the cancer cost by asking how much life shortening it produces before some given age. Murray and Axtell (1974) of the National Cancer Institute have looked at the "costs" to the United States economy for all the cases of cancer who died in one year. They found that by taking the average life span and finding how much of the working life has been lost by cancer victims and multiplying this by the average annual income for persons employed at that time, that one

year's death from cancer in the United States cost of the order of $18 billion dollars. They do not include medical costs, or any secondary costs to the families.

The problem of cost is not simple. The British Department of Welfare and Social Security (1972) asked the question, "Suppose we were able to reduce smoking in current British smokers by 20% or 40%, what would the net monetary effect be?" Up to sometime in the 1980's or 1990's there would be a net gain to the British economy, but following that there would be a net loss. The net loss would occur because those persons who had not died from their smoking-related diseases would live long enough to draw pensions and the costs of the pensions would exceed the contributions (monetary) that these persons would have made to society by extending their working lives. This particular example shows the problems of a quick look at a cost-benefit analysis. As persons get older in our population they are no longer producers and they cost something to our working population to keep them alive. A simplistic cost-benefit analysis taking this into account might consider that these persons were not of any particular worth. A logical conclusion from such a cost benefit analysis would say that these people are costing us more than the society is benefitting from them. Therefore, there is no good reason to keep them in the population at all. One wonders at this time whether one should take an Orwellian point of view and by carrying this cost-benefit analysis to its somewhat silly, logical extreme and see to it that people did not smoke but also to see to it that they died promptly at the age of 65 so that they would not draw any pensions. I'm not recommending this.

There has been substantial talk and little work done on the problems of cost-benefit with respect to materials that may be carcinogens that are added to our environment. There could be important gains from some of the food additives or some of the pesticides like DDT. Since these materials have great economic importance, an attempt has been made to equate the economic gains from increased food production following from using a pesticide, to the economic losses associated with illness and premature death from cancer. With respect to the cost-benefit computations, I think first, the "logical" results from the British Department of Welfare and Social Security should be kept in front of our faces. Second, the answers to Cornfield's question need to be considered openly. Cornfield asks the question "costs to whom and benefits to whom?" Are the costs and benefits to the same person? If the costs and benefits are not to the same person what action then is appropriate for societies to take? Is it appropriate for me to benefit by having my electric bill reduced at the expense of some workers in atomic energy electrical plants getting too high a dose of radiation and dying sooner?

There are many situations in which benefits might accrue to only one portion of the population and the costs to another portion of the population. What are society's responsibilities within this set of circumstances? Is society as a whole responsible since the benefits accrue to Society (now with a capital S)? Is Society responsible for ameliorating the costs? Does it mean that Society should pension off the family of the wage earner who had died early of a bladder cancer as a result of exposure to an industrial carcinogen which is used in making dyes from which all of us benefit by having the more brightly colored environment about us? Should this worker's family get a full pension equivalent to his income for the remainder of his working life that he may have lost? On a much lower scale, should all this worker's medical costs be born by "Society"? I put Society in capitals here because we must ask who makes up society? Is it the Federal Government, the local government, the community? We all pay for what some of us gain.

Finally, with respect to the cost-benefit problem in general, let me give a not-so-hypothetical example. Let us say that the American Cancer Society in its efforts to cut down deaths following smoking

develops an effective program in anti-smoking propaganda. Let us say that their program is effective in reaching young people and those other groups in the population that their older programs have not been so effective in reaching—the Blacks, the women, etc. This is a program that will have some economic costs—you and I contribute to the American Cancer Society and that's a cost. It will have some benefits. There will be people who will live longer, who will not die of lung cancer or perhaps cancer of the bladder, or one of the other things associated with smoking. Although the American Cancer Society is doing it, some of these people will not die of heart disease or emphysema or certain forms of bronchitis. And finally, some of the people will live long enough to get on the pension roles and remain there for a long time. To whom should these particular costs now be ascribed? On whose account do we check out that these things are costs? If the American Cancer Society's program is very successful it may be that there will be some industrial workers who are put out of jobs—people manufacturing cigarettes. It may be that the tobacco farmers will not be able to grow tobacco and not get that income. If they move from tobacco to say soybeans and get a higher income, should that be reckoned as a negative cost? I don't know the answer to any of these questions, but it seems to me that the cost-benefit problem is a very much more complicated one than we have realized in the past. It also seems to me that the problem of computing costs and benefits can not be left to people who are interested parties. I don't know in whose hands the computations ought to be put, but just as my first example on the problems of how one interprets the asbestos data indicated that the same set of data might very well be interpreted differently by different people, it also seems to me that the computations of costs and benefits will come out to be very different if done by different people. I'm not asking that statisticians be appointed (or anointed) to do these computations. Statisticians are no more free of their personal cultural histories than anyone else. Michael Polanyi (1969) pointed out many years ago that the scientific ideal of an absolute truth divorced from human judgment is worse than foolish—it also impedes scientific progress.

Thus, it seems to me that the problems of determination of "safe" dose are problems that transcend our field of statistics. They are problems that transcend the field of the laboratory worker; they are problems that transcend the field of the epidemiologist; they do not seem to me to be problems that can be solved even by those of us in the three fields working together. The problems of social costs which flow from our determination of "safe" doses require a whole group of other kinds of input. What then can be done to attempt to help assure that we have a safer society within which to live? I'd like to give two sets of recommendations—one from a colleague who has worked and thought about this problem at some length and one from a well-known geneticist. Here's what my first colleague says: "Do monitoring. Use registries and record linkage to detect sudden increases in space-time occurrence of the kinds of diseases we are concerned with. When followback reveals that these are due to some specific drug or chemical we are already in a bad situation. A great many people have already been exposed but at least the causative agent can be recognized and if it is then removed from the environment perhaps we can prevent an epidemic." The implementation of his suggestion requires that there be alert people, groups of experts looking all the time for these sudden increases or clusters. Many of the things reported as sudden increases or clusters will turn out to be dead ends, useless leads. This is comparable to the occasional breaking through the limits in a quality control chart and where we find nothing wrong, no departure in our process. Nonetheless, these unusual events will still have to be examined. They will have to be

investigated just as we do in quality control.

What about things that are not yet in the environment? We certainly must do animal testing. We must screen materials for carcinogenic effects in rodents and perhaps in higher animals. In spite of all the difficulties that Dr. Rall expressed in the last paper, we must pay substantial attention to these results. Materials that appear to be carcinogenic in these experiments will probably have to be excluded from the environment. Some exceptions probably will be made or can be made for drugs or related materials that are used to treat uniformly or rapidly fatal illnesses in which quite obviously the benefit to be gained by the person taking the drug will be very much greater than the cost of possible cancer to this person some years in the future. However, for materials in which the gain and benefits do not accrue to the same person it is likely that these materials will not be marketable. If it appears, however, that the material is of very great economic potential then obviously work on metabolism and biochemistry will have to be done. If it can be demonstrated that the material is metabolized substantially differently by the experimental animal than it is by man, then this would indicate thatwe must do further laboratory-animal research to find species in which metabolism is closer to that of man and do carcinogenic testing in them. If in such species we can demonstrate the identity of the metabolic pathway to man's and such species can demonstrate that the material is not a dangerous material, then obviously it becomes marketable. In addition we will have learned a great deal about the metabolism of different kinds of animal species. Finally, we obviously must encourage research into laboratory methods that will give us answers quickly as to possible positives. I think we have to develop some no-false negatives screening systems to cut down on the enormous number of materials that now seem to have to be tested in long-term life span animal feeding experiments. If quick methods can be developed that produce no-false negatives, even if the methods ask us to test five true negatives for every one positive they would introduce many economies in money and in time.

The second suggestion that should be taken quite seriously was made by James Crow (1973), the geneticist, in the publication of the National Institute of Environmental Health Sciences. Crow takes a lead from the work on radiation risks and with the so-called "allowable" increased dose of radiation permitted from sources such as the production of power through atomic energy. Crow notes that among the early maximum levels that were established by such groups as the BEIR group (1972) and others was an addition of radiation to the environment roughly equal to the amount that one naturally received from nature. Crow further suggests arithmetically converting the hazards from chemicals to a radiation equivalent dose, and setting this equal to the early "maximum" permissible addition, 170 millirems. In doing this we soon get into problems of the appropriate dose response curve at low levels; what are the incremental cancers that occur given this particular dose of chemicals? If we can make this chemical-radiation equivalence perhaps even crudely, Crow then recommends that we treat any new material entered into the environment as a potential additional "burden." If this added burden then brings us up over the equivalent of 170 millirems, then action must be taken to bring the total burden down to its allowable level. In other words if we introduce a new chemical into the environment and it is of such economic importance that it must be introduced, there then have to be other chemicals that will come out of the environment, since the new materials plus the old materials would bring us up above the maximum permissible additional burden. This would create a situation in which the people who manufactured and marketed the old material might be required to present information to demonstrate why their material should remain in the en-

vironment rather than permitting the new material to enter into the environment. And the promoters of the new material would have to present the contrary arguments. Under these circumstances there would be some healthy competition as to what new materials might come into the environment. It might very well influence a company which already has a substantial number of materials on the market to not introduce another one because the new one would require that an old one be taken out of sale. It might be a useful thing for the Shell Comapny, manufacturers of Dieldren, and the Montrose Chemical Company of California, the manufacturers of DDT, to present arguments as to which of the two (or either of them) might better remain in the environment.

There is something Crow neglects and that we have not talked about here today. It presents serious statistical problems. Crow's limit assumes that each additional material added to the environment has a simple additive effect. There is evidence that this is likely not to be true. To see this one has only to recall the experience of the smoking asbestos worker as compared to the asbestos worker who does not smoke or the smoker who does not work in asbestos factory or the smoking uranium miner as compared to the uranium miner who does not smoke and again the smoker who is not an uranium miner (Doll, 1971). If we can get multiplicative effects of smoking and asbestos exposure or smoking and radon exposure it may very well be that some of the environmental chemicals we have give us multiplicative rather than additive effects. These things obviously will have to be tested and we will have to see what combinations break through Crow's upper equivalent of 170 millirems. These problems of testing multiple materials for their additive non-linear interactions, are once again problems for the statisticians in designing the experiment and in evaluating the data.

In all these activities that the statistician has to participate, he can not go it alone. He is involved with the epidemiologist in the monitoring. He is involved with the computer people in helping develop data linkage systems. He is involved with the laboratory worker in setting up the animal screening systems and he is involved with the administor in evaluating the effectiveness of these animal screening systems. He is involved with helping set up and evaluate the quick laboratory methods. Thus, I see the statistician intimately and deeply involved with much more than just mathematical theory for setting "safe" doses. I see a great many research problems that need to be worked on. I see that these can not be worked in a statistical vacuum. I see problems of social values intruding on the scientists and intruding on the statistician. There is no way that these can be escaped. Perhaps the best thing that the statistician can do is to declare his loyalties and his biases and let people then evaluate the work he has done. Since I advocate that statisticians be open about their biases, I owe it to this audience to be open about mine. As I reviewed the data relating asbestos to cancer in the first part of this paper, it seemed that my bias in coming to you out of the field of cancer research certainly affected what I did with the data, how I handled them, and how I interpreted them. I, therefore, declare I am employed by the National Cancer Institute, an arm of the Federal Government, a research agency, and my personal bias is strongly against cancer.

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